REMARKS

Applicant respectfully requests entry of the foregoing amendments prior to continued examination of the application.

I. Status of the Claims

Claim 1 is amended to recite a specific embodiment described, for example, at page 10 of the specification as filed. Claims 10 and 12 and withdrawn claim 20 are amended to conform to the amendments to claim 1. Claim 13 is amended to depend from claim 1. Claims 23-30 are added to recite specific embodiments described, for example, at pages 10-11 of the specification as filed. Claims 4 and 14 are canceled without prejudice or disclaimer. Upon entry of the amendments, claims 1-3, 5-13, 15-21 and 23-28 will be pending. These claims are presented for examination.

Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application.

II. Status of Claims 13-21

On page 2 of the Advisory Action mailed July 7, 2006, the Examiner maintained the withdrawal of claims 13-21, stating that claims 13-21 are directed to a patentably distinct invention from claims 1-12. Notwithstanding this finding, Applicant urges rejoinder of claims 13-21 (and new claims 26-28) because once claims 1-12 are determined to be patentable, claims 13-21 and 26-28 will likewise be patentable, because they depend from claim 1.

III. Response to Rejections under 35 U.S.C. §103

The Advisory Action maintained the rejection of claims 1-10 and 12 for obviousness over U.S. patent No. 4,919,937 ("Mauvais-Jarvis"), as evidenced by Mauvais-Jarvis (1986), in view of Atkinson *et al.*, *Cancer Epidemiology, Biomarkers & Prevention*, 8: 863-866 (1999) ("Atkinson") as evidenced by Boyd *et al.*, *JNCI*, 87: 670-675 (1995) ("Boyd") and Kolb *et al.*, *Radiology*, 225: 165-175 (2002) ("Kolb"). Applicant respectfully traverses this rejection.

The primary reference, Mauvais-Jarvis, describes percutaneous administration of 4-hydroxy tamoxifen and documents the ability of 4-hydroxy tamoxifen to cross the cutaneous barrier. However, Mauvais-Jarvis does not teach or suggest that 4-hydroxy tamoxifen is effective for reducing breast density, as presently taught and claimed. Indeed, Mauvais-Jarvis provides no basis for predicting the usefulness of 4-hydroxy tamoxifen in the present methods.

The secondary reference, Atkinson, doesn't even relate to 4-hydroxy tamoxifen or to transdermal administration. It allegedly teaches that oral tamoxifen reduces mammographic breast density, but it misses the mark on both the active agent and the mode of administration. Neither Boyd nor Kolb remedy the deficiencies of Mauvais-Jarvis and Atkinson. Indeed, there is no evidence of record that 4-hydroxy tamoxifen was expected to be useful for reducing breast density, let alone that it would have the same effect on breast density as oral tamoxifen.

The rejection relies on the premise that because both "tamoxifen and 4-hydroxy tamoxifen have been individually taught in the prior art to be effective at treating conditions of the breast, including . . . cancer," then "[o]ne of ordinary skill in the art would have a reasonable expectation of success that by administering 4-hydroxy tamoxifen percutaneously . . . one would achieve [a] method of reducing breast density." But Applicant has shown that position to be unsupported by the record, and contrary to the state of the art.

Tamoxifen and 4-hydroxy tamoxifen have been shown to have varying effects in the same tissues and cells. Several examples of these varying effects have been documented in the literature. For instance, tamoxifen but not 4-hydroxy tamoxifen is a potent rat liver carcinogen. See Carthew *et al.*, *Archives of Toxicology*, 75: 375-380 (2001), and Sauvez *et al.*, *Carcinogenesis*, 20(5): 843-850 (1999), both already of record. Additionally, tamoxifen but not 4-hydroxy tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells. See Dietze *et al.*, *J. Biological Chemistry*, 276(7): 5384-5394 (2001) (already of record). By contrast, 4-hydroxy tamoxifen exhibits a significant inhibitory effect on estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little or no effect in this regard. See Chetrite *et al.*, *Anticancer Research*, 13: 931-934 (1993), already of record.

Thus, the usefulness of 4-hydroxy tamoxifen in methods where tamoxifen has proven useful is not predictable.

In the absence of any prior art evidencing a reasonable basis for expecting percutaneously delivered 4-hydroxy tamoxifen to have the same effect on breast density as tamoxifen, the obviousness rejection is improper and should be withdrawn.

The Examiner also maintained the rejection of claim 11 for obviousness over the combination of Mauvais-Jarvis in view of Atkinson as evidenced by Boyd and Kolb and further in view of Tan *et al.*, *AAPS PharmSciTech*, 1, Article 24, (2000) ("Tan"), and Alberti *et al., J. Controlled Release*, 71: 319-327 (2001) ("Alberti"). Tan allegedly teaches the use of hydrophilic polymers, including Carbopol and hydroxypropyl cellulose, to improve bioadhesive properties. Alberti allegedly teaches the topical delivery of terbinafine using a vehicle consisting of ethanol and isopropyl myristate. As described in a prior response, however, neither Tan nor Alberti compensates for the deficiencies of Mauvais-Jarvis, Atkinson and the other art, explained above. Accordingly, claim 11 also should be allowed.

Applicant notes further that the instant claims recite a pharmaceutical composition for percutaneous administration comprising 4-hydroxy tamoxifen and isopropyl myristate. While Applicant believes that the previously presented claims are patentable for the reasons set forth above, Applicant urges the further patentability of the instant claims because the cited references do not teach or suggest methods using a composition for percutaneous administration comprising 4-hydroxy tamoxifen and isopropyl myristate.

IV. Concluding Remarks

Applicant believes that this application is in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issues remain, the Examiner is invited to contact the undersigned attorney by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extension of time is needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

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